

2011 Military Health System Conference

Advances in Translational Medical Research

The Quadruple Aim: Working Together, Achieving Success

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January 25, 2011



Congressionally Directed
Medical Research Programs

Mission and Vision



Mission

We provide hope by promoting innovative research, recognizing untapped opportunities, creating partnerships, and guarding the public trust.

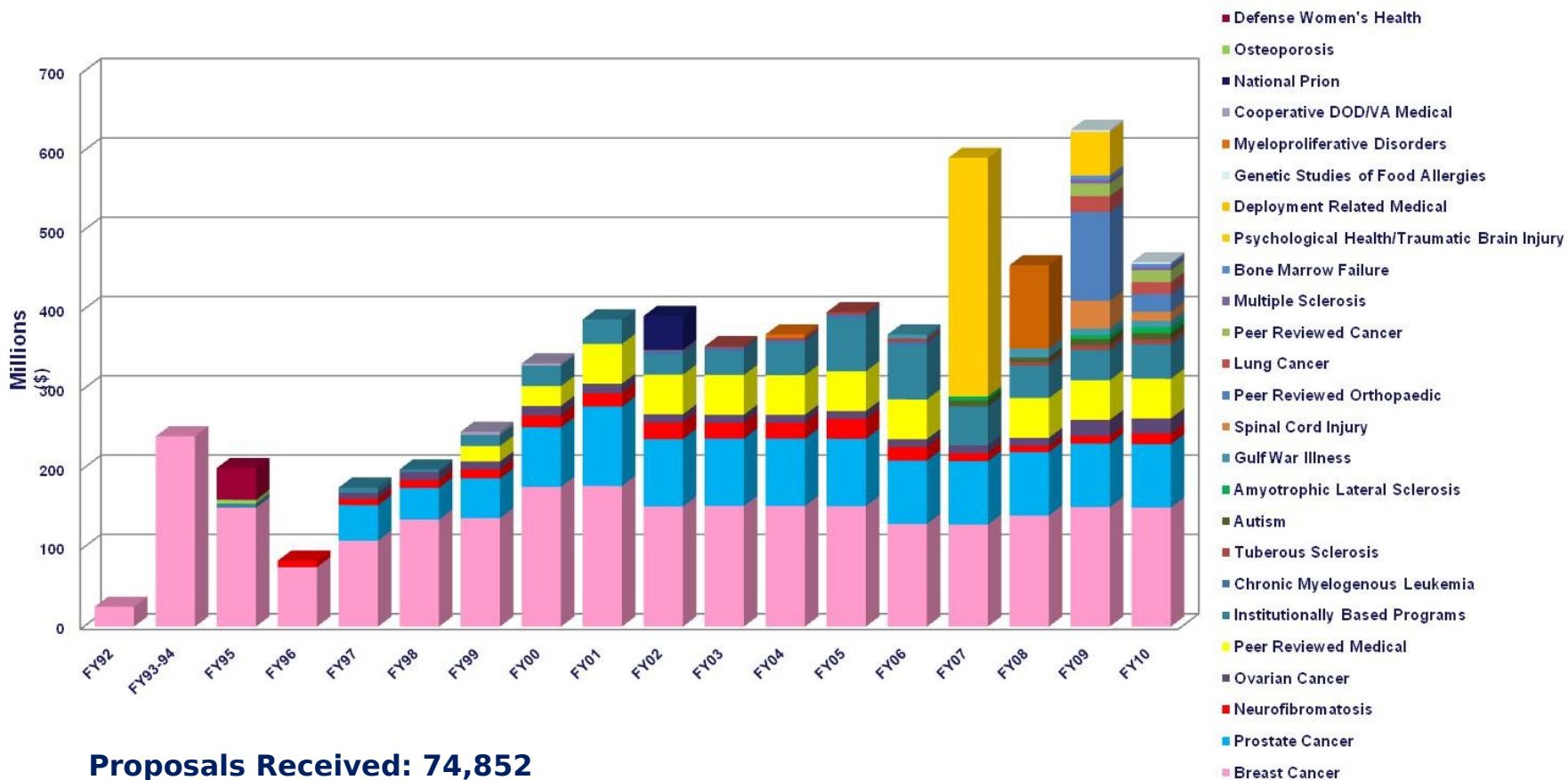
Vision

Find and fund the best research to eradicate diseases and support the warfighter for the benefit of the American public.

Program History



Scope of CDMRP Funds and Awards



Proposals Received: 74,852

Grants Funded: 10,409

As of 12-17-2010

CDMRP Unique Features



- Disease-specific research funds added to DoD budget by Congress
- Vision is adapted yearly, and award mechanisms are changed as needed
- Two-tier formal review of proposals – Institute of Medicine model
- Consumer advocates involved throughout process
- Fund highly innovative research
- Unique peer review:
 - No standing panels
 - No contact between reviewers and applicants
- Funding flexibility
 - No “pay line;” funding recommendations based on portfolio balance, innovation, and impact
 - Funds obligated up front; no out-year budget commitments
 - No continuation funding



CDMRP Partnerships



Advocates

- ◆ Demonstrate need
- ◆ Participate at all levels
- ◆ Passion and perspective



Congress

- ◆ Add funds to budget
- ◆ Targeted guidance
- ◆ Opportunity to leverage



**IMPROVE
HEALTH
(CURE)**

Researchers

- ◆ Innovation and gaps
- ◆ Risk/Benefit
- ◆ Product-oriented

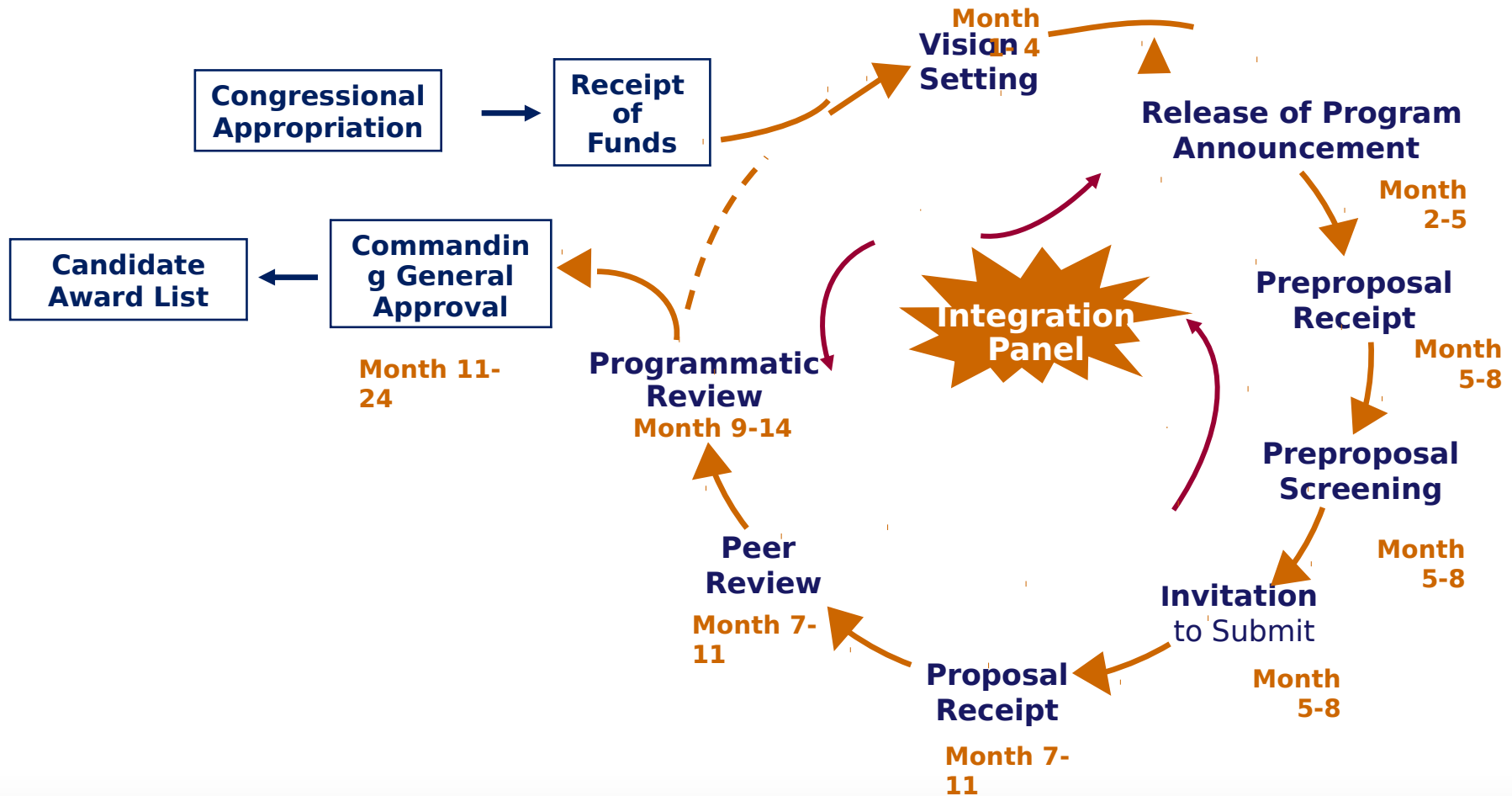


DoD

- ◆ Program management
- ◆ Regulatory and budget requirements
- ◆ Institute Of Medicine model



CDMRP Program Cycle



Innovative Two-Tier Review Process



Goal: To **find** scientifically meritorious and innovative proposals, and **fund** those that best fulfill program goals



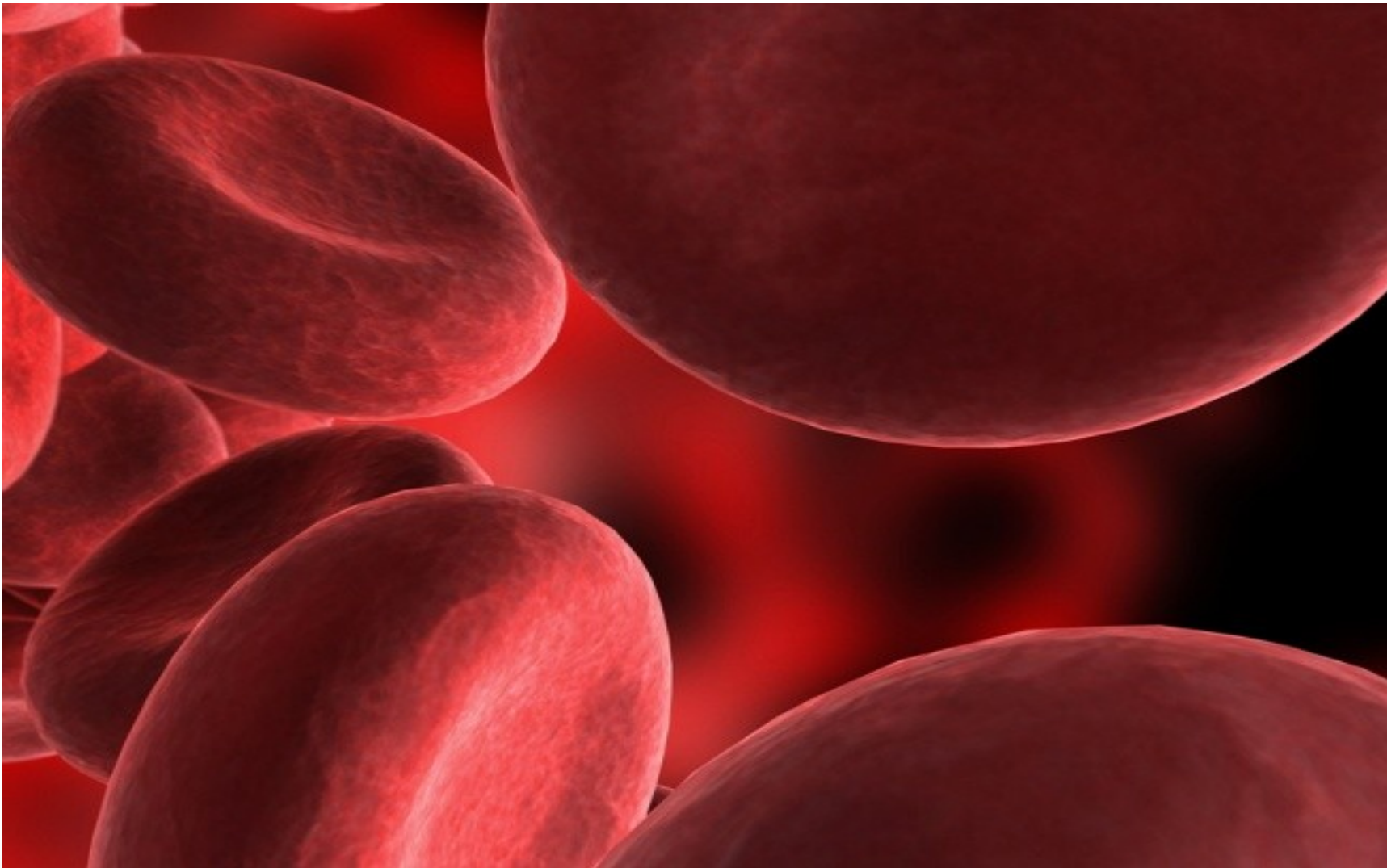
- Peer Review
 - Evaluation of scientific merit
 - Criteria-based evaluation
 - Proposals evaluated within related disciplines
- Products:
 - Proposal scoring
 - Summary statements
- Programmatic Review
 - Evaluation of programmatic relevance
 - Comparison-based evaluation
 - Proposals evaluated across multiple disciplines
- Product:
 - List of funding recommendations for the Commanding General, USAMRMC

What Does the CDMRP Fund?



- Innovative, high-risk/high-gain research that can leapfrog advancements
- New collaborations and partnerships
- Research to improve patient/survivor quality of life
- Future innovators and leaders in the field
- Research to answer current needs
- Research to define and reduce health disparities

High-Risk/High-Gain Research



High Risk/High Gain: Herceptin



FY93 BCRP Investigator-Initiated Research Award

Dr. Dennis Slamon, UCLA

- Examined the mechanism of action of Herceptin, a humanized monoclonal antibody, against the *Her2/neu* receptor
- Herceptin is the first humanized antibody approved for treatment of Her2-positive metastatic breast cancer (Genentech; 1998)
- Herceptin is now standard of care for the adjuvant treatment of early-stage Her2-positive breast cancer
- Phase II clinical trials are in progress for non-small lung cancer, acute lymphoblastic leukemia, and ovarian cancer



Dr. Slamon's research efforts led to the making of a Lifetime Television movie, "Living Proof"

Collaborations and Partnerships



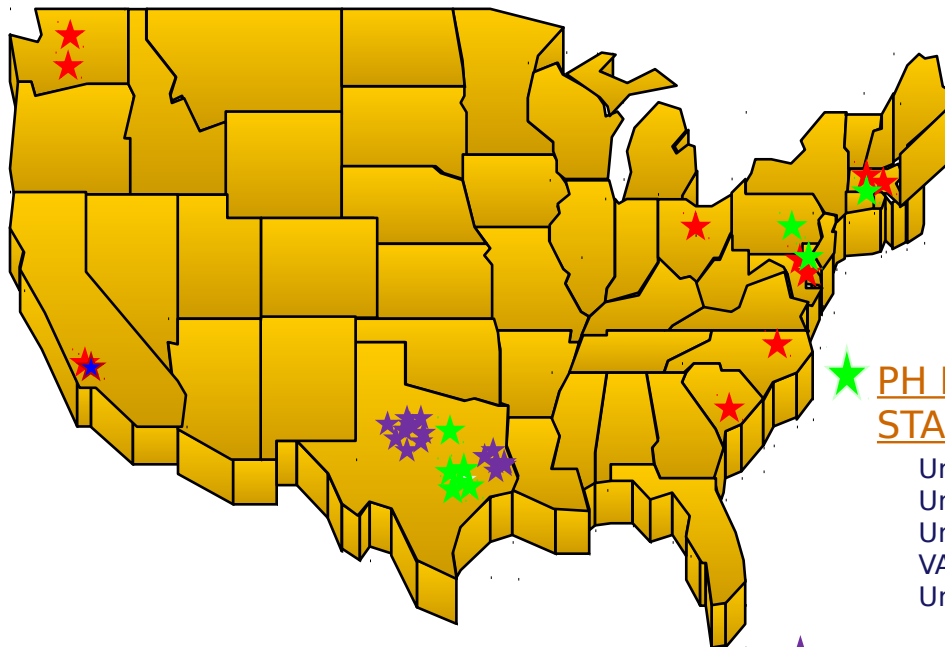
CDMRP PH and TBI Consortia



PH/TBI Clinical Consortium: INJury & TRAumatic STress Consortium (INTRuST)

★ Clinical Consortium Coordinating Center
University of California, San Diego

★ Clinical Consortium Study Sites
University of Maryland, Baltimore
Uniformed Services University of the Health Sciences
Spaulding Rehabilitation Hospital
Dartmouth College
University of Washington
University of Cincinnati
Duke University
University of California, San Diego
Medical University of South Carolina
Madigan Army Medical Center



★ PH Multidisciplinary Research Consortia (STRONG STAR)

University of Texas Health Science Center at San Antonio
University of Pennsylvania
University of Texas at Arlington
VA Boston Healthcare System
Uniformed Services University of the Health Sciences

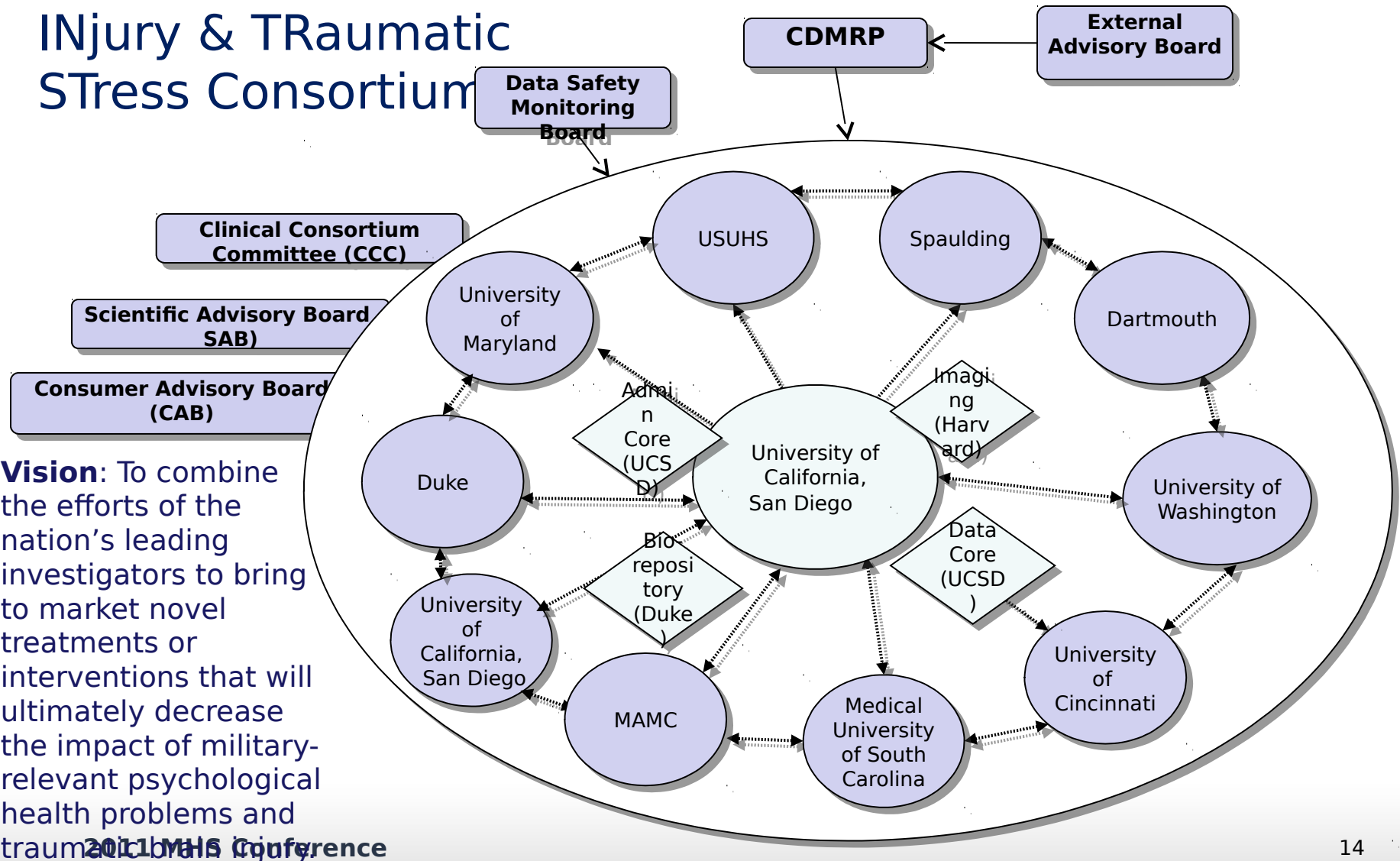
★ TBI Multidisciplinary Research Consortia

University of Texas Health Science Center at Houston
Baylor College of Medicine
Rice University
University of Galveston
Transitional Learning Center at Galveston



Partnerships: INTRuST

Injury & TRaumatic STress Consortium



INTRuST Studies



Main Studies

- Proof-of-Concept Trial of Ganaxolone in PTSD
- Effects of Telephone Follow-up on Outcome for Service Members with mTBI/PTSD
- Randomized Clinical Trial of Glyburide for TBI
- Initial Randomized Controlled Trial of ACT for Distress and Impairment in OEF/OIF Veterans
- Randomized Controlled Trial of Galantamine, Methylphenidate, and Placebo for the Treatment of Cognitive Symptoms in Patients with mTBI and/or PTSD
- Brain Indices of Risk for PTSD after mTBI
- A Pilot Safety and Feasibility Study of High Dose Left Prefrontal Transcranial Magnetic Stimulation to Rapidly Stabilize Suicidal Patients with PTSD

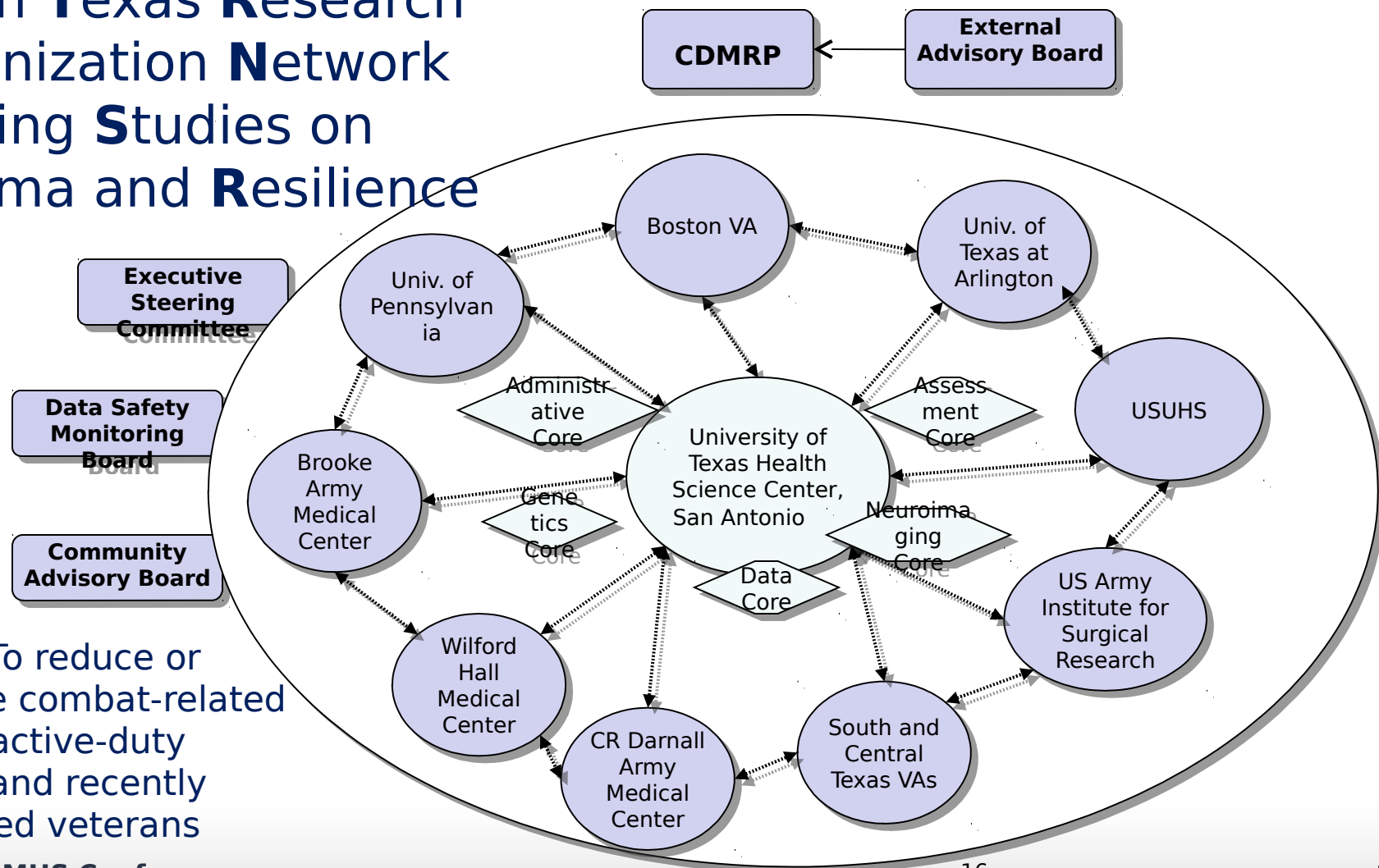
Pilot Studies

- A Double-Blind, Placebo-Controlled, Flexible-Dose Pilot Clinical Trial of Once-Daily Extended-Release Tramadol for the Treatment of PTSD
- Novel Functional and Structural Biomarkers of Neuroinflammation and White Matter Change in TBI: A Potential New Diagnostic and Therapeutic Approach
- Improving Walking and Balance in Veterans with TBI
- Exercise: A Novel Treatment for Combat PTSD
- Cardiovascular Risk Markers in Veterans with PTSD
- The Use of Qualitative Methods to Support Clinical Trial Studies in PTSD-TBI Research
- Reliability and Initial Validation of the INTRuST Structured Clinical Interview for TBI in the Military Setting (SAFE-TBI)

Collaborations: STRONG STAR



South Texas Research Organization Network Guiding Studies on Trauma and Resilience



Vision: To reduce or eliminate combat-related PTSD in active-duty military and recently discharged veterans

STRONG STAR Projects



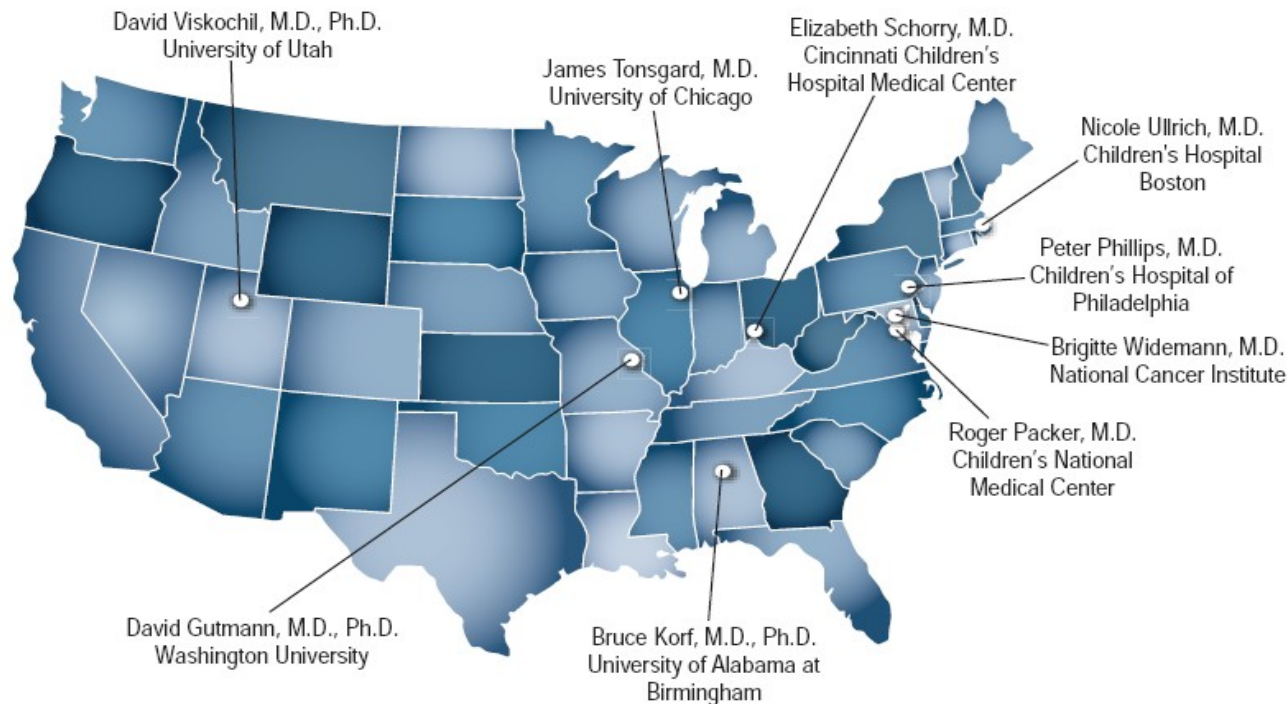
- **Outcomes of Prolonged Exposure and Cognitive Processing Therapy used in the Treatment of Combat Operational Stress Reactions in Deployed Settings**
- **Prolonged Exposure Treatment for PTSD Symptoms in Primary Care Settings**
- **Prolonged Exposure for PTSD among OIF/OEF Personnel: Massed vs. Spaced Trials**
- **Cognitive Processing Therapy for Combat-Related PTSD**
- **Individual PE vs. Couples' Cognitive-Behavioral Therapy for Combat-Related PTSD**
- **Treatment of Chronic Stress Reaction and Chronic Pain after Traumatic Orthopedic Injury: A Randomized Clinical Trial**
- **Prolonged Exposure Therapy for PTSD in Burn Patients**
- **Alcohol Use Disorder in PTSD Patients Treated with SSRI's: An Alcoholic Subtype Hypothesis of Vulnerability**
- **Prevalence of Fibromyalgia in PTSD Patients and Family Members**
- **The Impact of the Treatment of PTSD on Comorbid Insomnia and Pain**
- **Neuroimaging Studies of PTSD and PTSD Treatment among Combat Veterans**
- **Who gets better and why? Predicting Outcome Trajectories in STRONG STAR Trials**
- **Genetic and Environmental Predictors of Combat-Related PTSD**
- **Longitudinal Examination of Changes in Hypothalamic Pituitary Adrenal (HPA) Axis Responses to Stress in Military Subjects**

Collaboration: Prostate Cancer Clinical Trials Consortium



- Goal:** Develop the infrastructure to increase patient accrual to Phase I/ II clinical trials and expedite bringing better therapies to patients.
- 13 cooperating sites increase trial accessibility and rate of completion
 - Have recruited more than 2,300 patients
 - More than 10% of patients are from minority populations
 - Have conducted 83 Phase I/II or Phase II studies
 - Have investigated 50+ drugs
 - Eight potential new therapies have moved into Phase III trials

Collaborations & Partnerships: Neurofibromatosis Clinical Trials Consortium



- Phase II trial of Sirolimus (rapamycin) for the treatment of plexiform neurofibromas in patients with NF1
- Phase II study of lovastatin for the treatment of NF1-associated learning and memory impairments
- Phase II study of Everolimus (RAD001) for treatment of low grade gliomas

Quality of Life



Quality of Life: Hybrid Neuroprosthesis

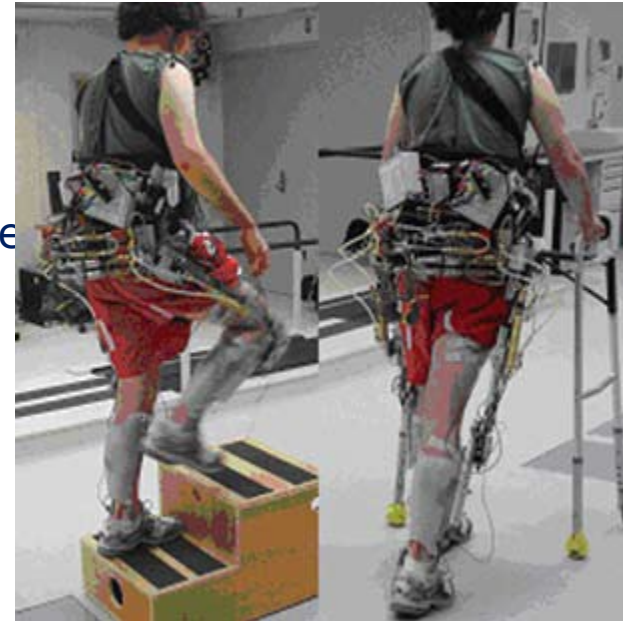


FY04 PRMRP Investigator-Initiated Award

Dr. Ronald Triolo, Case Western Reserve

Prototype Hybrid Neuroprosthesis

- Provide the means to stand, walk, climb steps and exercise
- Prevent or reverse deleterious effects of paralysis
- Prototype hybrid neuroprosthesis that enhances personal mobility for paraplegics:
 - Exoskeletal bracing
 - Implanted functional electrical stimulation
 - Braces lock and unlock joints so walking can be more fluid and natural
- Prototype pilot study:
 - Paraplegic and able-bodied volunteers
 - Paraplegic evaluation (one subject): exoskeletal bracing heavy, but provided functional support



Quality of Life: Hybrid Neuroprosthesis



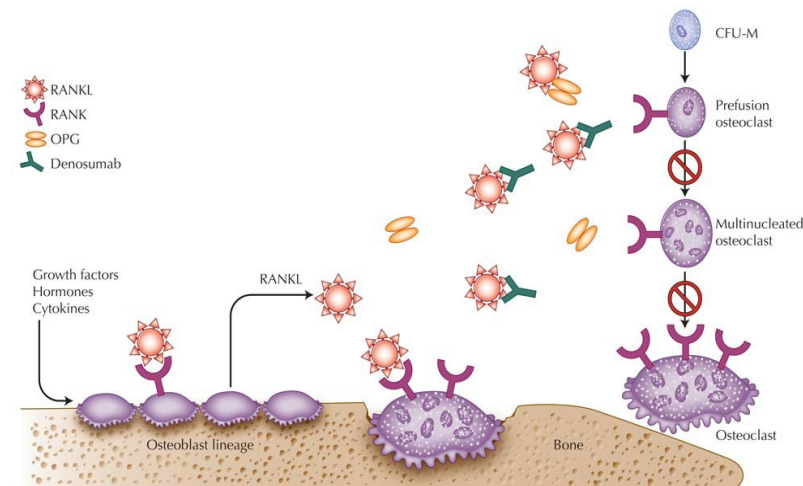
Quality of Life: Denosumab



FY02 PCRP Idea Development Award Dr. Evan Keller University of Michigan



- Preclinical studies funded by CDMRP found that blocking the activity RANKL (receptor activator of NFκB ligand) is effective in diminishing progression of prostate cancer growth in bones
- These RANKL studies led to the development of denosumab, a monoclonal antibody against RANKL
- Denosumab is currently being studied in 26 Phase III clinical trials across a range of conditions including osteoporosis, cancer treatment-induced bone loss (e.g. hormone ablation), bone metastases, multiple myeloma and rheumatoid arthritis
- In November 2010, the FDA approved denosumab for treatment of bone loss during cancer based on three independent studies that showed it was more effective than the standard of care
- XGEVA™ for cancer and Prolia™ for osteoporosis are now available to patients



Quality of Life: Prazosin



FY07 PH-TBI Research Program

Dr. Murray Raskind

Seattle Institute for Biomedical and Clinical Research

Got Nightmares?

- In a small, open-label study, Prazosin appeared to reduce debilitating trauma nightmares in Service Members who had deployed to Iraq
- Military physicians have been prescribing Prazosin to soldiers in combat since 2005
- Approximately 26,000 Vietnam veterans are already taking Prazosin for chronic PTSD
- This study will develop an effective pharmacologic treatment to reduce the disabling morbidity of chronic PTSD in this new generation of combat veterans
- Study Trials have been conducted at the VA Puget Sound, Madigan Army Medical Center and Walter Reed Army Medical Center
- **2011 MHS Conference**
Ongoing recruitment at Madigan Army Medical Center

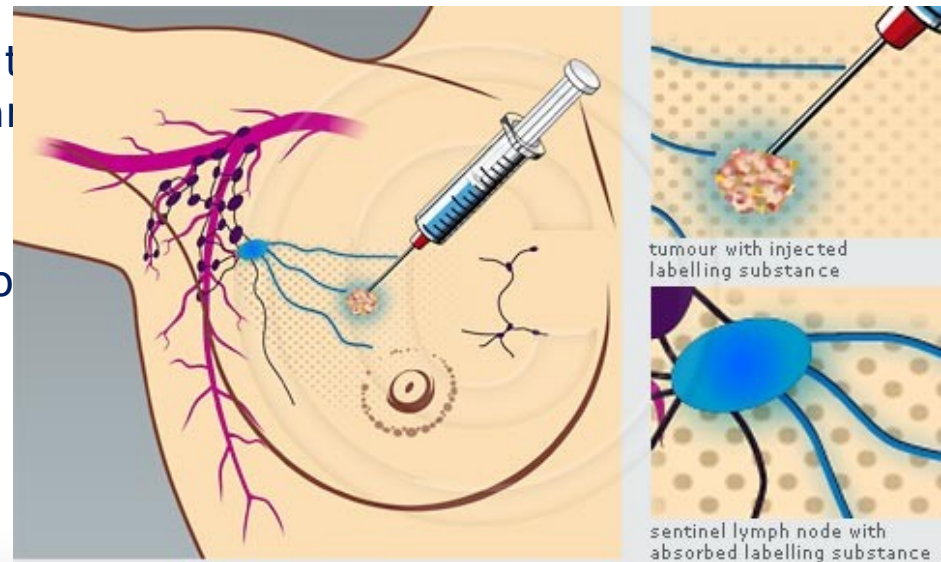
Quality of Life: Sentinel Lymph Node Biopsy



FY97 BCRP Career Development Award and FY99 BCRP Clinical Translational Research Award

**Dr. Kathryn Verbanac
East Carolina University**

- Supported a multi-center clinical trial testing the validity and accuracy of sentinel lymph node biopsy in predicting the spread of disease
- Accurately identifying the first nodes that receive lymph drainage allowed for a change in practice
- Results of the clinical trial contributed to what is now the current standard of care for breast cancer staging
- Also identified prognostic markers in sentinel node metastases by RT-PCR to improve accuracy of staging by pathology alone



Innovators and Leaders



Innovation: Sniffing Dogs



FY06 OCRP Idea Development Award

Dr. Touradi Solouki
University of Maine

- Exhaled breath condensate (EBC) is used as a source of biomarkers that may distinguish women with ovarian cancer from healthy controls
- Trained dogs can “sniff out” ovarian cancer in EBC with 97% accuracy
- EBC is analyzed by Gas Chromatography Fourier Transform Ion Cyclotron Resonance Mass Spectrometry (GC/FT-ICR MS) to identify biomarkers
- End result: a “breathprint”



Photos courtesy of Drs. Michael McCulloch and Touradj Solouki

Heffner C, Silwal I, Peckenham JM, Solouki T. 2007. *Environ Sci Technol* 41(15):5419-5425.

J. E. Szulejko, M. McCulloch, J. Jackson, D. McKee, J. Walker, **T. Solouki**, “Evidence for Cancer Biomarkers in Exhaled Breath –

A Review” *IEEE Sensors J* 10 (1) 185-210 **2010**

Innovation: Sniffing Dogs



A superb bioinformatic approach

- Uses excellent analytical capabilities to sift through myriad of signals for correct identification!
- Excellent brain power that exceeds current bioinformatic capabilities to filter noise and make sense of “real” data and hidden correlations!

An incredible detection system

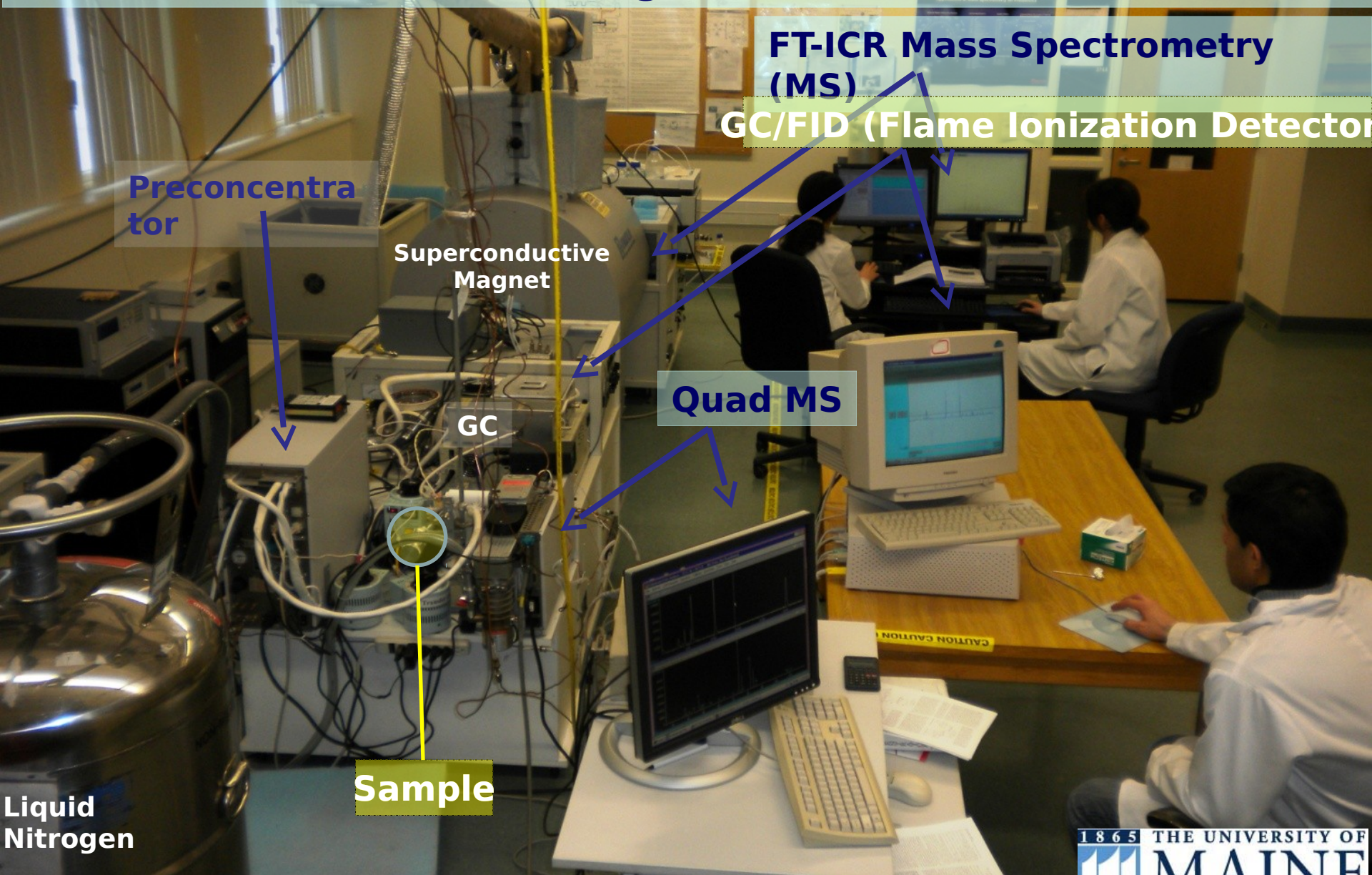
- Contains thousands of sensors
- 10,000 to 100,000-times more sensitive than humans
- Threshold sensitivity: one part per trillion (1ppt)
- Uses a large volume sample size
- Uses biological pre concentration approach
- **Can we capture information as sensitive as a Dog's Nose? Yes, with individual compounds! The developed technology can be used to resolve complex mixtures containing thousands of chemicals!**



Photos courtesy of Drs. Michael McCulloch and Touradj Solouki

D.B. Walker et al. / Applied Animal Behaviour Science 97 (2006) 241-254

A full room of equipment and personnel to approximate A Dog's Nose!



Special program - National Geographic Channel: Fall 2011

Innovation: Sleep Management System



FY99 PRMRP Investigator Initiated Award

Dr. Gregory Belenky, WRAIR

Wristwatch Actigraph

- Problem: Sleep loss (total sleep deprivation and sleep restriction for operational realities) impairs cognitive readiness
- Solution: Sleep as an item of re-supply
- Device measures how much sleep you have on hand and estimates current cognitive readiness



Warfighter at 100%
Good to go
for at least
16 more hours



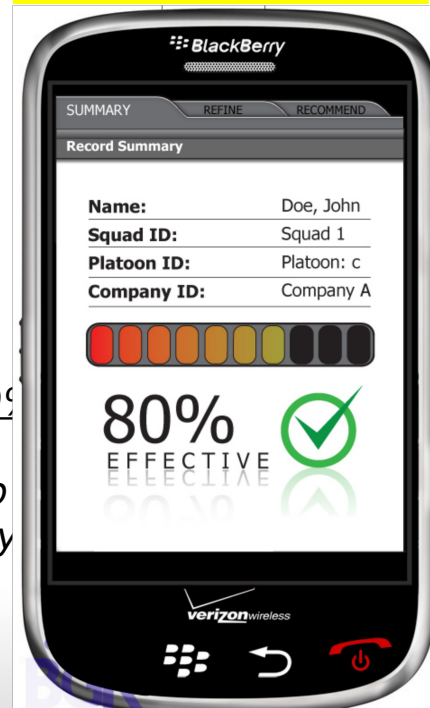
Warfighter at 60%
Good to go
for 12-16 more hours
with countermeasure
(e.g., caffeine)



Warfighter at 40%
Good to go
for 6 more hours
with countermeasure
(e.g., caffeine)



Warfighter at 0%
Needs at least
6 hours of sleep
to return to duty



Answer Current Needs



Answer Current Needs: Early Detection of Ovarian Cancer



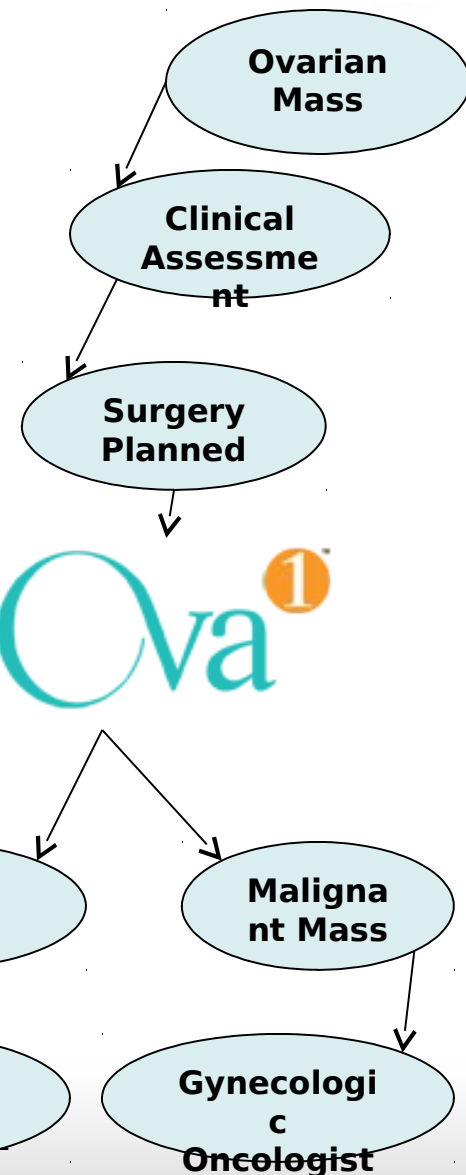
FY03 OCRP Idea Development Award

Dr. Zhen Zhang

Johns Hopkins University

- Dr. Zhang discovered and validated a panel of ovarian cancer biomarkers for the early detection of ovarian cancer
- Based on his findings, Dr. Zhang and colleagues at Johns Hopkins University, in collaboration with Vermillion Inc., developed the OVA1 test to help physicians detect ovarian cancer in a woman with a pelvic mass prior to surgery
- OVA1 is the only FDA-approved blood test to help determine if an ovarian mass is malignant or benign
- OVA1 may help a doctor determine the type of surgery to whom the patient should be referred
- In a double-blind clinical trial with dual assessment (pre-surgical assessment and OVA1), sensitivity for malignancy was 92%, compared to 72% without OVA1

2011 MHS Conference



Answer Current Needs: “Escape With Your Life”



FY04 Institution-Based Research Program - Lung Cancer

Dr. Alexander V. Prokhorov, M.D., Ph.D.

M.D. Anderson Cancer Center



- Video game developed to educate teens on causes of lung cancer
- Encouraged stopping – or not starting – smoking
- More than 50% of study participants quit smoking at 6 months after playing the video game
- Awarded funding through Peer Reviewed Medical Research Program to modify game for use in military facilities

Answer Current Needs: Neurofibromatosis Mouse Models



FY01 NFRP Therapeutic Development Award

Dr. Kevin Shannon

University of California, San Francisco

- Major effort to generate mouse models of NF1 and NF2
- These models did not exist prior to CDMRP grant funding
- NF Mouse Models Consortium generated accurate models of many NF1- and NF2-associated tumors:
 - Plexiform Neurofibroma
 - Malignant Peripheral Nerve Sheath Tumor
 - Glioma
 - Meningioma
 - Myeloid Leukemia
- Mouse models have been provided to more than 50 laboratories worldwide



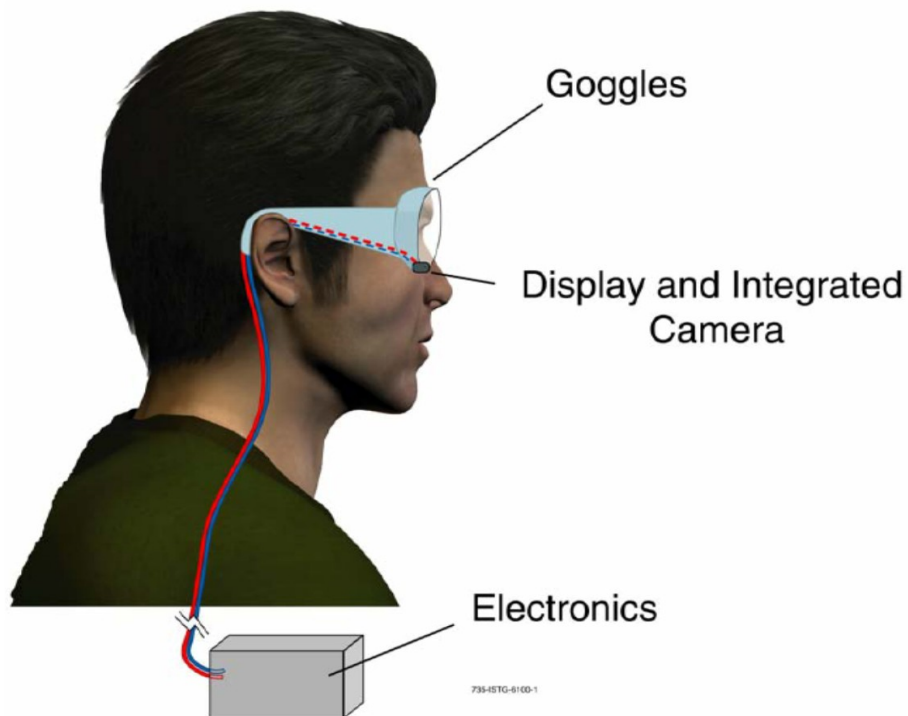
Answer Current Needs: Early Diagnosis of mTBI



FY07 TBI Advanced Technology-Therapeutic Development Award

Dr. Jamshid Ghajar, Brain Trauma Foundation, Inc.

Eye-Tracking Rapid Attention Computation

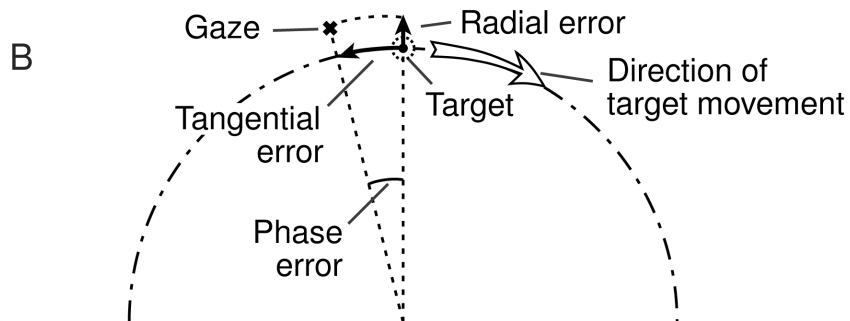
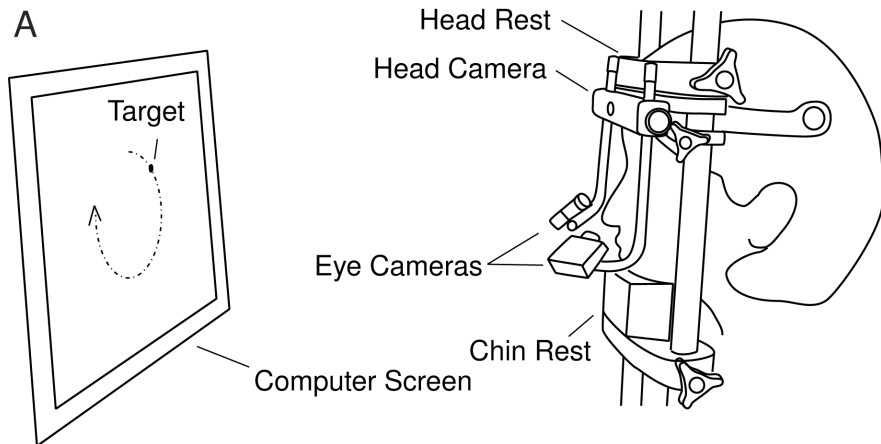


- Mild TBI (mTBI) is difficult to diagnose
- EYE-TRAC will facilitate rapid diagnosis in theatre to identify Service Members with injury related complications that could have a negative impact on unit performance
- EYE-TRAC requires less than 30 seconds to measure
- Device accurately measures millisecond eye-target synchronization in predictable smooth pursuit eye movements
- Cohorts are fatigued soldiers, normal aging population, mTBI, ADHD, normal soldiers
- Software development underway to help distinguish between mTBI and PTSD

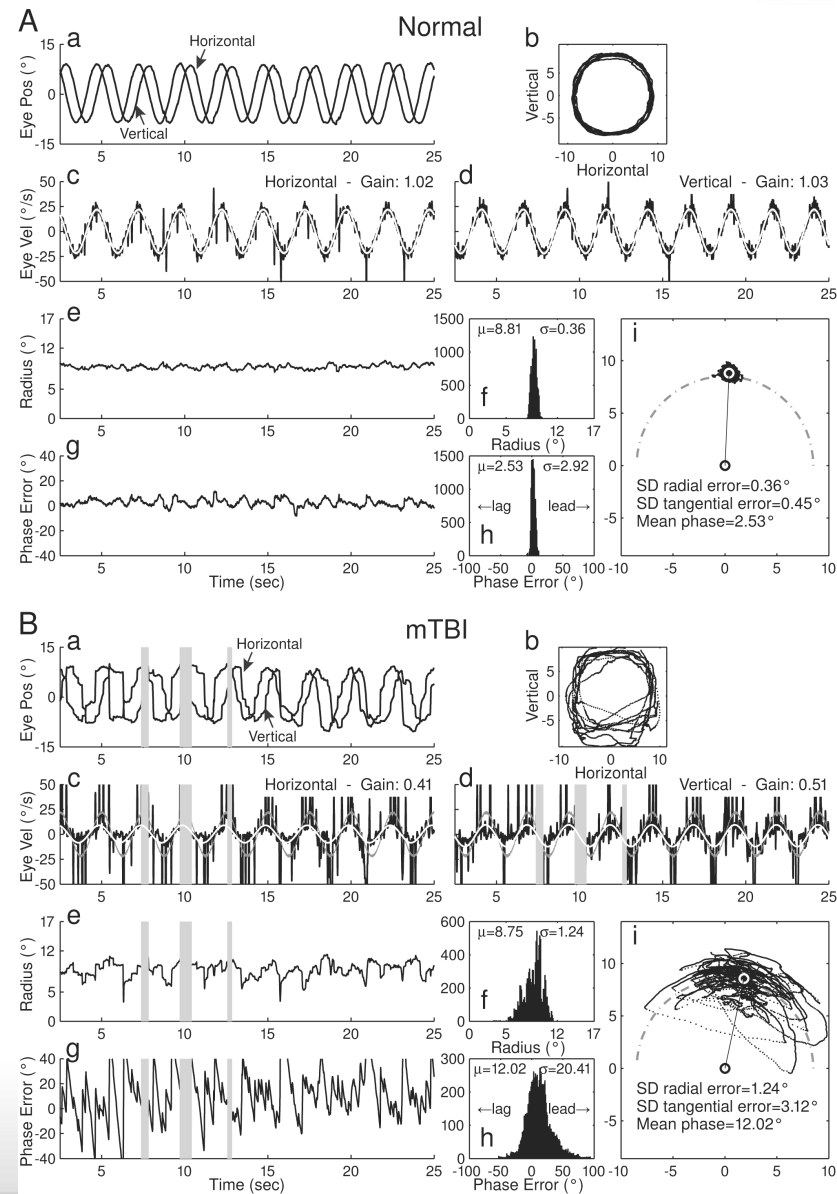
Answer Current Needs: Early Diagnosis of mTBI



EyeTRAC Pilot Data Statistical difference in radial and tangential tracking in persons with TBI vs controls



2011 MHS Conference



Define and Reduce Health Disparities



Reduce Health Disparity: Prostate Cancer Project (PCaP) Consort

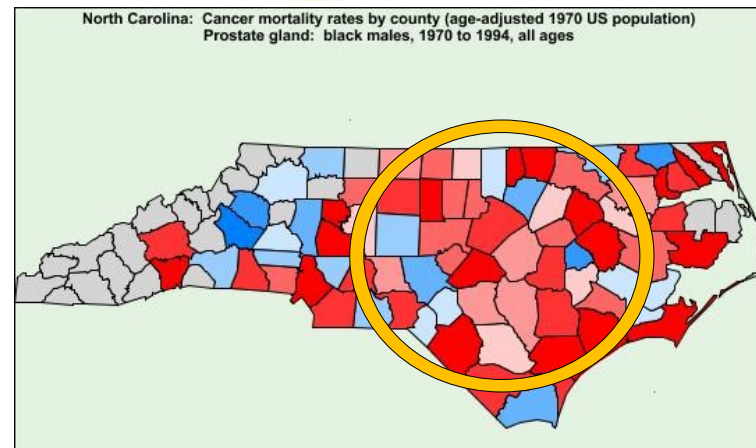
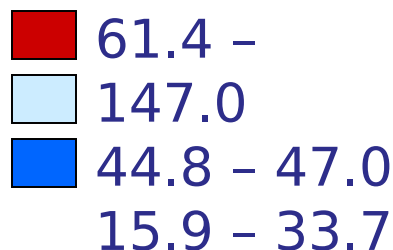
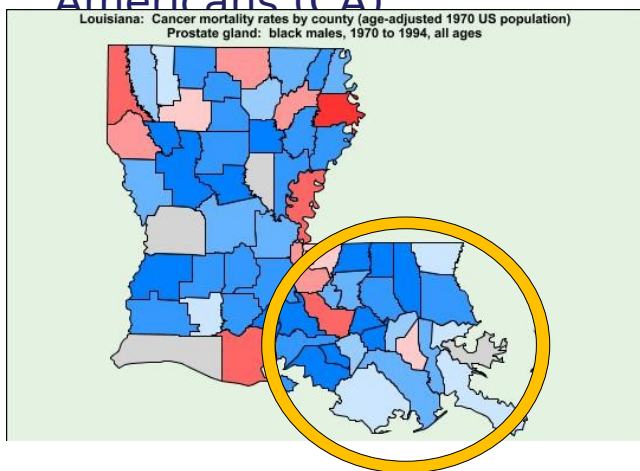


FY02 PCRP Consortium Award

James Mohler, M.D.

Roswell Park Cancer Institute

- In men under 65 years of age, the PCa mortality rate for African Americans (AA) is **3.1** times that of Caucasian Americans (CA)



Mortality / 100,000 Black Males 1970-1994

US: 47.2 (46.9 – 47.5)

LA: 42.2 (41.0 – 43.5)

NC: 55.4 (54.0 – 56.8)

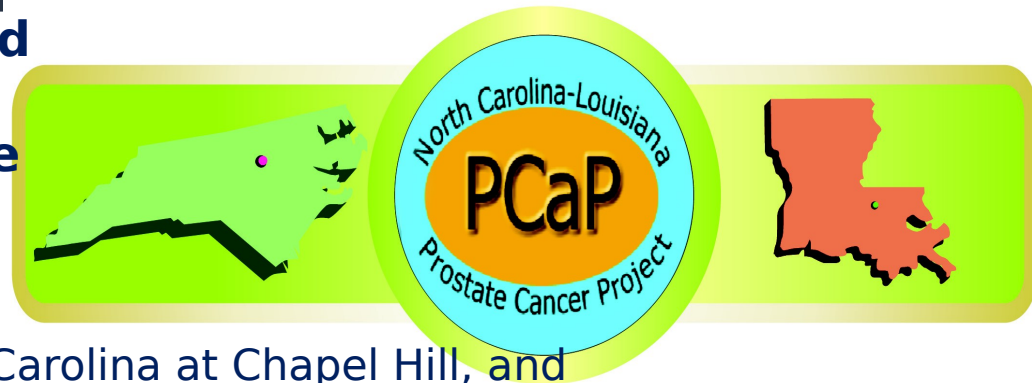
Reduce Health Disparity: Prostate Cancer Project (PCaP) Consortium



FY02 PCRP Consortium Award

James Mohler, M.D.

Roswell Park Cancer Institute



- A consortium was developed by Roswell Park Cancer Institute, the University of North Carolina at Chapel Hill, and the Louisiana State University Health Science Center to study contributing factors to this health disparity, including:
 - limitations in access to health care due to socioeconomic status
 - treatment decision-making due to race- or culture-based factors
 - racial differences in tumor biology due to genetic or environmental factors (e.g. diet)
- More than 2,000 AA and CA men participated in the study
- AA men diagnosed with PCa tended to be younger, have less income and education, and have less effective interactions with health care providers than CA counterparts
- An unprecedented database of epidemiological data and biospecimens was generated for use by the wider PCa research community to answer disparity-related questions

From our Consumer Advocates



“The whirlwind of CDMRP experience is challenging, enlightening, and inspiring from a personal and professional level. As a survivor, I am impressed with the researchers and love that they enjoy being able to meet people like me, patients who will be impacted the most by their efforts to eradicate cancer.”

“CDMRP is a vital link in the chain of events that will eventually bring relief to tens of thousands of American heroes. I am honored to be afforded the opportunity to play a role in that noble undertaking.”

“The people I have met and work alongside as a Consumer Reviewer for CDMRP are among the smartest and most compassionate medical professionals I have ever met. I am proud to be a small part of this truly incredible group that has the well-being of the many, for many generations to come, at heart.”

CDMRP - Providing Hope



<http://cdmrp.army.mil/>

